

Case Reports

THE TREATMENT OF ACUTE FULMINANT HEPATITIS WITH CORTICOTROPIN AND CORTISONE*

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SINCE THEIR INTRODUCTION as therapeutic agents, corticotropin and cortisone have been utilized in many diseases of diverse etiology, sometimes with a rational basis and sometimes without. In general, it may be stated that new uses for these hormones have been found either by analogy with diseases in which they have been effective, or in cases in which they have been used as a last resort when all other therapeutic measures have failed. It was therefore natural to attempt to determine their effect in hepatic disease, whether chronic, acute or fulminant. As early as 1950, Webster¹ reported his experiences in nine cases of various forms of acute and subacute liver disease with "extract of adrenal cortex." All nine patients recovered promptly and laboratory tests rapidly reverted to normal after treatment. Re-examination after a year revealed no evidence of liver dysfunction, even in those with a history of chronic liver disease. In 1951, Colbert and others² described their results in five cases of acute viral hepatitis, given 100 mg. of ACTH daily for periods of 9-21 days. They reported that marked symptomatic improvement occurred promptly and was associated in all instances with a falling serum bilirubin concentration. There has been some difference of opinion, however, as to the value of corticotropin and adrenal cortical steroids in portal cirrhosis. Helm³ reported satisfactory results in a 53-year-old woman with Laennec's cirrhosis, who was in critical condition when first seen, and made a highly satisfactory recovery, apparently as the result of cortisone therapy. On the other hand, in a study of 10 patients with advanced portal cirrhosis, Sklar and Young⁴ were unable to discern any significant benefit from the use of corticotropin and corticoids in high dosage. Some of these patients were in hepatic coma or pre-

coma, while others showed evidence of liver failure without coma. All these patients died, and none showed even transitory benefit. An unexpected observation in this study was the failure of treatment to produce even the usual non-specific effects on mood and appetite. It is distinctly possible that, when hepatic failure supervenes in a patient with advanced chronic liver disease, even such potent therapeutic agents as these may be of no value. However, it appears likely that, in acute hepatic disease, even when it has progressed to the stage of hepatic failure, the pathological changes may be reversible, and recovery may be brought about by the use of these hormones. As is usually the case, careful and controlled studies have somewhat limited the enthusiasm with which these therapeutic agents were originally greeted in the treatment of liver disease. A series of such studies by Evans and others⁵⁻⁷ appeared to indicate that corticotropin is of very little value in acute and chronic hepatic disease, that cortisone may be of some value in acute disease but not in fulminant cases, and that these hormones may leave patients more vulnerable to relapses. Nevertheless, when large numbers of patients with infectious hepatitis were subsequently treated with cortisone, using adequate controls,⁸ this form of treatment was found to be of distinct value. The results of this particular study indicated that cortisone causes a more rapid clearing of jaundice than occurs in controls, that laboratory findings tend to return to normal faster, and that such patients on cortisone therapy regain their appetite sooner, eat more food and gain more weight than is the case in controls. The data in this study also indicate that cortisone-treated patients become well sooner and do not require treatment so long. It would therefore appear that patients who do not respond to the usual supportive measures, or whose recovery with such measures is in doubt, should certainly be given a trial on corticotropin or cortisone or both.

The case reported below is one of acute fulminant hepatitis in which the onset of hepatic coma was suspected, and in which dramatic improvement and eventual complete recovery resulted from the use of both these hormones.

Mrs. S.A., 58 years of age, was admitted to the City of Sydney Hospital on January 13, 1955, complaining of jaundice. Her previous history was not contributory. She had been previously attended by one of us (A.R.G.) for "nervousness", and on the day of admission had called this physician, complaining of jaundice. She was imme-

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diately transferred to hospital, where physical examination was completely negative with the exception of rather deep icterus and a large tender liver, felt four fingerbreadths below the right costal margin. A clinical diagnosis of infectious hepatitis had been made, and the patient was placed on a high protein, high carbohydrate, low fat diet. Examination of the blood revealed a haemoglobin value of 13.7 g. per 100 c.c., a red cell count of 4,980,000 and a white cell count of 7,300 per c.mm. The differential count was within normal limits. The blood sugar was 101 mg. per 100 c.c., the blood urea was 28 mg. per 100 c.c. and the urea nitrogen was 13 mg. The icterus index was 90. The blood group was found to be O, Rh positive. The serum bilirubin was 20 mg. per 100 c.c. The prothrombin concentration was 50% of normal. Urinalysis revealed a specific gravity of 1.019, a trace of albumin, a 4+ reaction for sugar (patient had been receiving intravenous glucose), a trace of acetone and a 4+ test for bile. Microscopic examination revealed a few white blood cells and an occasional red blood cell. Examination of the stool for occult blood gave a 4+ test. The cephalin flocculation test was 4+ on two occasions.

For the next 48 hours, the patient's condition progressively deteriorated, and one of us (S.J.S.) was called in consultation on January 15. At that time, the physical findings were essentially the same as had been the case 48 hours earlier, but, at this time, signs of impending hepatic coma were noted, in that the patient was semi-stuporous, difficult to arouse, and irrational when it was possible to gain her attention. In addition, the liver edge was now five fingerbreadths below the costal margin, there was evidence of ascites, and there were large ecchymoses scattered over the entire body surface. Vaginal bleeding was also noted.

The diagnosis of infectious hepatitis was concurred in, but it was felt that we were dealing with either a fulminant case of this disease or with an acute hepatic necrosis, presumably of viral origin. After prolonged discussion, it was decided to continue with supportive measures, but that, if no improvement was evident within 24 hours, corticotropin should be considered. On the following day no improvement was noted, and corticotropin was started in a dosage of 40 mg. intravenously every eight hours in 500 c.c. normal saline. In addition, aureomycin was administered in a dosage of 250 mg. every four hours, blood transfusions were begun, and synthetic vitamin K was given in 50 mg. doses daily.

Over the next 72 hours, there was gradual and continued improvement in the patient's condition, and she was seen again in consultation (S.J.S.) on January 20, 1955. At that time her general condition appeared dramatically improved as compared with that on January 15. Her sensorium was far less clouded, and the liver was distinctly smaller, being now three fingerbreadths below the right costal margin. This latter finding was not necessarily considered a sign of improvement. However, whereas there had previously been a degree of oedema of the extremities, this was now no longer present. The pulse was 80 per minute, and of good quality. The blood pressure was 130/80 mm. Hg. At this point, it was felt that striking improvement had taken place, but the final outcome was still in doubt.

The dose of corticotropin was gradually decreased, and hydrocortisone was begun in doses of 200 mg. daily, in such a manner that for a period of 2½ days the patient was receiving both corticotropin and hydrocortisone. The patient was continued on a high protein, high carbohydrate diet, with supplementary potassium chloride in doses of 6.0 g. daily. The transfusions and the vitamin K were also continued. During the next few days, the laboratory findings gradually returned to normal as the clinical condition improved, although the cephalin flocculation test remained abnormal. The remainder of the patient's course was uneventful, and she was discharged to her home, without jaundice and clinically well, on February 24, 1955.

DISCUSSION

There seems to be little doubt that this patient was in, or entering, the state of hepatic coma, when she was seen on January 15; and it seems difficult to attribute her dramatic recovery to any medication other than the corticotropin and cortisone. There is a distinct possibility, however, that the use of aureomycin may have influenced the satisfactory outcome. Farquhar and others⁹ reported four cases of acute hepatic coma, all of which recovered following aureomycin therapy, and they attributed the satisfactory result to the use of aureomycin. We have, however, been unable to corroborate this finding by a rather extensive search of the literature, and the weight of evidence seems to be in favour of the hormones as the major agents in bringing about recovery in this case. It might have been wiser and more scientific to use one agent or the other (i.e. either aureomycin or hormones); but the patient's condition was felt to be so precarious that it was considered unwise to temporize. Moreover, in certain circles, it is always considered desirable to use a broad-spectrum antibiotic in all seriously ill patients in which large doses of corticotropin or cortisone or both are being given.

It would seem reasonable, therefore, to consider the use of corticotropin or cortisone or both in patients seriously ill with infectious hepatitis who are not responding to the usual supportive measures. It would also seem wise in such cases to combine a broad-spectrum antibiotic, preferably aureomycin, with the hormonal therapy. We do not, however, advocate hormonal therapy in all cases of infectious hepatitis since, in our experience, most of these patients recover satisfactorily without specific treatment.

SUMMARY

1. A case of acute fulminant infectious hepatitis with hepatic coma is reported, in which dramatic improvement and final recovery followed the use of corticotropin and cortisone.
2. It is possible that the patient's recovery was influenced by concomitant treatment with aureomycin; but the weight of evidence is in favour of the hormones as the major agents in bringing about recovery.
3. It is recommended that corticotropin or cortisone or both be used in cases of severe infectious hepatitis which do not respond to supportive measures.

4. The recent literature on this subject is reviewed.

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HEPATO-LENTICULAR DEGENERATION

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IT IS USUAL for some degree of liver damage to be present in chronic heart disease. In advising management for the heart the requirements of the liver should be considered, and its further injury by such factors as over-digitalization, anoxia and alcoholism should be avoided if possible. The following case is reported because lenticular degeneration was found at autopsy in a man who had suffered from chronic heart disease, from liver infections, and also from the causes of liver damage mentioned above.

A 32-year-old veteran of World War II, with no family history of liver disease or of other relevant illness, fell sick at the age of 20 years with malaria. He was serving in Italy at the time, and on being evacuated to a hospital in North Africa he was also discovered to have mitral stenosis in spite of a negative history of rheumatic infection or of heart trouble.

He recovered from the malaria and returned to duty, but two years later, just before being discharged from the Army, he had an attack of infectious hepatitis. This illness took an uneventful course and again he recovered, but subsequently he was repeatedly admitted to D.V.A. hospitals with complaints of precordial pain, dyspnoea, fatigue, hæmoptysis and joint pains. At this time he was going from one job to another; he was drinking heavily and was estranged from his wife. Because he seemed to be using the hospitals as emotional sanctuaries, he was labelled in 1948 as an inadequate personality and in this assessment his war service seems to have been overlooked.

In 1952, when he was 30 years old, he developed acute pulmonary oedema and while he was in hospital he was found to have subacute bacterial endocarditis. He was regarded as a difficult patient, being unstable, immature and poorly disciplined, and he was now diagnosed as a psychopathic personality. A second admission to hospital was necessary in 1952, when he was suffering from the effects of several arterial emboli. He also had considerable anorexia, nausea and vomiting.

He lost much weight. In 1953 he was admitted on three occasions for the control of various degrees of congestive heart failure precipitated by his omission to take digitalis because of his whim or of his alcoholic bouts. Sometimes his liver was noticed to be enlarged, and on a fourth admission in that year, liver function tests indicated functional insufficiency; the bromsulphalein retention was 22% in an hour, the thymol turbidity was 3 units, the thymol flocculation + + +, and the cephalin flocculation + +. A blood sugar level at this time was 50 mg. %. On this admission, besides the deterioration in his personality which had already been recorded by the change in diagnosis from inadequacy in 1948 to psychopathy in 1952, definite neurological signs were made out. These were a tonus increase and a comparative immobility of the left arm, but the tendon jerks remained unaltered and the patient was capable of moving the arm when his attention was distracted.

In January 1954, a mitral valvulotomy was performed. He did well for four days after the operation, but unfortunately bacterial endocarditis supervened and he went downhill in spite of intensive antibiotic therapy. An electrocardiogram in February 1954 revealed digitalis overdosage. He refused food and fluids; his hæmoglobin level fell 45%; he became jaundiced and comatose. Glutamic acid brought about a temporary improvement, but he died in March 1954.

At autopsy the right lenticular nucleus was found to be softened and microscopic section showed a liquefaction necrosis without inflammatory reaction (Fig. 1). The rest of the brain was normal. The liver was granular and on section showed interspersed hæmorrhagic and pale areas. It weighed 1,990 g. Microscopically the appearances were those of subacute yellow atrophy, with congestion, marked parenchymatous degeneration, and a moderate increase in the fibrous trabeculae (Fig. 2). The heart weighed 450 g.; a fibrinous pericarditis was present and the mitral valve was calcified and extremely narrow.

The copper content of the liver was found to be 0.50 µg. per g., a total of 100 mg. copper. This is less than the normal.

DISCUSSION

When Wilson described the syndrome of hepato-lenticular degeneration, he said that he thought the hepatic disorder preceded the cerebral damage, and since that time evidence has accumulated that in both man and animals degeneration of the basal ganglia is liable to occur as a result of severe and long-standing liver damage.^{1, 5, 9, 10, 16, 18} In the case described here, there were several factors which can reasonably be implicated in the production of such damage. The insults to the integrity of the liver included malaria and infectious hepatitis; malnutrition, anoxia, hypoglycaemia; and over-digitalization. There were also at work the effects of the mitral lesion. Liver function tests become abnormal in rheumatic heart disease¹¹ and also in heart failure. The development of central lobular necrosis resulting from anoxia and hepatic congestion to diffuse hepatic fibrosis has been traced by means of serial biopsies and by necropsy examination.¹⁵ Paul White has drawn attention to the atrophic and regenerative areas which occur after years of venous congestion,